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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12N 15/70, 15/31, 1/21, C07K 14/285,</b> <b>A61K 31/70, 38/16</b>		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/20609</b>
			<b>(43) International Publication Date:</b> 13 April 2000 (13.04.00)
<b>(21) International Application Number:</b> PCT/CA99/00938			<b>(74) Agent:</b> STEWART, Michael, I.; Sim & McBurney, 6th floor, 330 University Avenue, Toronto, Ontario M5G 1R7 (CA).
<b>(22) International Filing Date:</b> 7 October 1999 (07.10.99)			
<b>(30) Priority Data:</b> 09/167,568 7 October 1998 (07.10.98) US 09/206,942 8 December 1998 (08.12.98) US			<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
<b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 09/167,568 (CIP) Filed on 7 October 1998 (07.10.98)			<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(71) Applicant (for all designated States except US):</b> CONNAUGHT LABORATORIES LIMITED [CA/CA]; 1755 Steeles Avenue, Toronto, Ontario M2R 3T4 (CA).			<b>(88) Date of publication of the international search report:</b> 3 August 2000 (03.08.00)
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LOOSMORE, Sheena, M. [CA/CA]; 70 Crawford Rose Drive, Aurora, Ontario L4G 4R4 (CA). YANG, Yan-Ping [CA/CA]; Apartment 709, 120 Torresdale Avenue, Willowdale, Ontario M2R 3N7 (CA). KLEIN, Michel, H. [CA/CA]; 16 Munro Boulevard, Willowdale, Ontario M2P 1B9 (CA).			
<b>(54) Title:</b> PROTECTIVE RECOMBINANT HAEMOPHILUS INFLUENZAE HIGH MOLECULAR WEIGHT PROTEINS			
<b>(57) Abstract</b> <p>Protective high molecular weight (HMW) proteins are produced recombinantly by expression from <i>E. coli</i> by using a promoter effective in <i>E. coli</i> and a nucleic acid molecule which contains a modified operon of a non-typeable strain of <i>Haemophilus</i>. The modified operon contains the portion only of the A region which encodes the mature HMW protein and the complete B and C regions of the operon. Enhanced levels of expression of the HMW proteins can be achieved by including the <i>E. coli</i> <i>cer</i> gene, a further copy of the portion of the A region of the operon encoding the mature protein or both, in the expression vector. Nucleotide and deduced amino acid sequences of the <i>hmw1</i> and <i>hmw2</i> genes and HMW1 and HMW2 proteins, respectively, of several non-typeable <i>Haemophilus influenzae</i> strain have been identified.</p>			

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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>1038-985 MIS</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 99/ 00938</b>	International filing date (day/month/year) <b>07/10/1999</b>	(Earliest) Priority Date (day/month/year) <b>07/10/1998</b>
Applicant <b>CONNAUGHT LABORATORIES LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 99/00938

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 30,31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
  
1-36 (inventions 1,2,3)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-11, 13-16, 32-36) - completely; (18-20, 25-31) - partly

A nucleic acid molecule comprising a promoter functional in *E. coli* and operatively coupled to a modified operon of a non-typeable strain of *Haemophilus* comprising A, B, C genes, wherein the A gene of the operon contains only a nucleic acid sequence which codes for a mature high molecular weight protein of the non-typeable strain of *Haemophilus*.

Use in immunogenic composition and vaccine formulations.

2. Claims: (18-20) - partly

A plasmid vector for the expression of a high molecular weight protein of a non-typeable strain of *Haemophilus* and comprising a T7 promoter, a cloning site for the insertion of a nucleic acid molecule into the plasmid, and the portion B and C of the operon of a non-typeable strain of *Haemophilus*.

3. Claims: (12, 17, 21-31) - partly

An isolated and purified nucleic acid molecule encoding a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae*; a corresponding isolated, immunologically protective protein; corresponding immunogenic compositions and vaccine formulations,

WHEREIN the non-typeable strain of *Haemophilus influenzae* is Joyc (seq. IDs 25-32).

4. Claims: (12, 17, 21-31) - partly

Idem as subject-matter 3, but limited to strain K21 (seq. IDs 33-41).

5. Claims: (12, 17, 21-31) - partly

Idem as subject-matter 3, but limited to strain LCC2 (seq. IDs 42-49).

6. Claims: (12, 17, 21-31) - partly

Idem as subject-matter 3, but limited to strain PMH1 (seq. IDs 50-57).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: (12, 17, 21-31) - partly

Idem as subject-matter 3, but limited to strain PMH15 (seq.  
IDs 58-65).

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00938

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/70 C12N1/31 C12N1/21 C07K14/285 A61K31/70  
A61K38/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 36914 A (BARENKAMP STEPHEN J) 9 October 1997 (1997-10-09) cited in the application abstract examples 1-10	17,18, 21,22, 25-31
Y		19,20 1-16,23, 24,32-36
A	---	-/--

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

18 May 2000

Date of mailing of the international search report

05.06.00

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BARENKAMP S.J.: "Immunization with High-Molecular-Weight adhesion proteins of nontypeable Haemophilus influenzae modifies experimental otitis media in chinchillas"</p> <p>INF. IMMUN., vol. 64, no. 4, April 1996 (1996-04), pages 1245-1251, XP002133637 cited in the application the whole document</p>	17,21, 22,25-31
X	<p>-----</p> <p>BARENKAMP S J ET AL: "GENES ENCODING HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS OF NONTYPEABLE HAEMOPHILUS INFLUENZAE ARE PART OF GENE CLUSTERS"</p> <p>INFECTION AND IMMUNITY,US,AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 62, no. 8, 1 August 1994 (1994-08-01), pages 3320-3328, XP000578342 ISSN: 0019-9567 cited in the application the whole document</p>	17,21, 22,25-31
X	<p>-----</p> <p>WO 94 21290 A (BARENKAMP STEPHEN J ;ST GEME JOSEPH WILLIAM III (US)) 29 September 1994 (1994-09-29) abstract examples 1-6</p>	17,21, 22,25-31
X	<p>-----</p> <p>WO 93 19090 A (BARENKAMP STEPHEN J) 30 September 1993 (1993-09-30) cited in the application abstract examples 1-7</p>	17,21, 22,25-31
X	<p>-----</p> <p>ST. GEME III, J.W. ET AL.: "Secretion of the Haemophilus influenzae HMW1 and HMW2 adhesins involves a periplasmic intermediate and requires the HMWB and HMWC proteins."</p> <p>MOL. MICROBIOL., vol. 27, no. 3, February 1998 (1998-02), pages 617-630, XP000892544 cited in the application the whole document</p>	18
Y	<p>-----</p> <p>EP 0 502 637 A (ICI PLC) 9 September 1992 (1992-09-09) abstract</p> <p>-----</p> <p style="text-align: center;">-/--</p>	19,20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DAWID S.R. ET AL.: "High Molecular Weight adhesins of nontypeable Haemophilus influenzae: characterization of a novel mechanism of regulation" ABSTRACTS OF THE 1998 GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 98, 17 May 1998 (1998-05-17), page 74 XP002133638 cited in the application the whole document	18-20
A	ST. GEME III J.W. ET AL.: "Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable Haemophilus influenzae" INFECTION AND IMMUNITY, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 the whole document	12,17, 21-31

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00938

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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